REMARKS

Claims 9-12 are pending in the present application and are rejected. Applicants thank Examiners Shen and Bertoglio for the courtesies extended in the telephone interview of January 11, 2008. Applicants' Statement of the Substance of the Interview is incorporated herein.

Applicants' Response to Claim Rejections under 35 U.S.C. §102

Claims 9-12 were rejected under 35 U.S.C. §102(a) and 102(e) as being anticipated by Kumta et al. (U.S. Patent Application Publication No. 2003/0219466).

It is the position of the Office Action that Kumta discloses the invention as claimed. This rejection is maintained from the previous Office Action. Kumta is directed at a method of manufacturing hydroxyapatite and uses therefor in delivery of nucleic acids. Kumta is primarily directed at the manufacturing of hydroxyapatite. However, Kumta also discusses complexing hydroxyapatite with a biomaterial. As discussed in paragraph [0022], "the biomaterial is plasmid DNA that contains a gene, such as a bone morphogenic protein gene." Kumta also identifies rhBMP-2, Osx, Runx2 (also known as Cbfa1), PDGF, NGF, VEGF, IGF, FDFs, EGF, TGF-β, and BMP-7.

In the Amendment filed on August 1, 2007, claim 9 was amended to require "a bioadaptable porous material on which an adenoviral vector carrying a gene encoding an osteo-inducible transcription factor Cbfa1 *is adsorbed.*" In response to this amendment, the Office Action quotes the passage of the specification at page 7, lines 10-15. The Office Action thus states that "the breadth of claims 9-12 of instant application, in light of the specification,

encompasses the adenoviral vector carrying a gene encoding Cbfa1, which is conjugated in the hydroxyapatite nano particle, as taught by Kumta et al."

Because Applicants did not understand how the Office Action arrived at this conclusion, Applicants contacted the Examiner by telephone on November 16, 2007. Based on the Examiner's comments, it appears that he took an overly broad interpretation of the word "adsorb." The Examiner stated that this term is used in many references in different ways, and could refer to any two items coming together with each other in any way. The specification states that "vectors may be chemically bound to the bioadaptable materials, *or* they may be merely physically adsorbed thereon." Page 7, lines 12-13 (emphasis added). Applicants' representative explained that adsorption was a specific manner of interaction between the vector and the bioadaptable material, and that the amendment of claim 9 to recite adsorption excludes chemically binding vectors to the bioadaptable material. The Examiner was interpreting the term "adsorb" to encompass both (i) adsorbing vectors onto a bioadaptable material and (ii) chemically binding vectors to a bioadaptable material.

However, in view of the discussion in the telephone interview of January 11, 2008, the Examiner agreed that the term "adsorb" should be interpreted in view of the dictionary definition of the term. "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005) (*en banc*). The ordinary and customary meaning of a term may be evidenced by a variety of sources, including "the words of the claims

themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1327. See MPEP 2111.01. A copy of the dictionary definition is attached hereto.

According to the Mc-Graw Hill Dictionary of Scientific and Technical Terms, "adsorption" is "The surface retention of solid, liquid, or gas molecules, atoms or ions by a solid or liquid, as opposed to absorption, the penetration of substances into the bulk of the liquid or solid." Please see the attached definition, which Applicants submit as extrinsic evidence of the plain meaning of the term "adsorption" (and the term "adsorb").

In view of such a definition of the term "adsorb," Applicants respectfully submit that Kumta does not disclose or suggest the embodiment as recited by claim 9. As discussed above, in Kumta, the vector is complexed with hydroxyapatite. See paragraph [0117], which discloses that "nanocrystalline hydroxyapatite particles complexed with plasmid DNA harboring a BMP-2 gene." This "complexing" is analogous to chemically binding a vector to a bioadaptable material. As such, the vector would appear to be dispersed approximately evenly within the hydroxyapatite particles. On the other hand, if a vector is adsorbed on the hydroxyapatite particles, the vector would be concentrated on the surface of the hydroxyapatite particles. Thus, Applicants respectfully submit that the implant as recited by claim 9 is structurally distinguishable over that of Kumta.

With respect to claims 10-12 reciting of β-TCP, Applicants previously submitted that Kumta only refers to β-TCP in the context of analysis of the hydroxyapatite manufacturing process. The Office Action responds by stating that "Kumta et al. clearly indicate the

composition and chemical relationship of hydroxyapatite and β-TCP in the context of using these bioadaptable porous material for delivery of nucleic acid." The Office Action cites Example 1, paragraphs [0053] and paragraphs [0074]-[0094]. However, this example only deals with synthesis of hydroxyapatite, and does not discuss plasmid delivery.

In response, as discussed in the telephone interview of January 11, 2008, Applicants respectfully reiterate that Kumta only discusses β-TCP in the context of a byproduct of degradation of hydroxyapatite. As disclosed in paragraph [0086]: "[h]ydroxyapatite decompose into β-TCP and CaO accompanied by slight weight loss which is difficult to detect via TGA." There is no suggestion or disclosure of a β-TCP bioadaptable material comprising an adenovirus carrying a gene encoding Cbfa1, whether the vector is adsorbed onto a β-TCP bioadaptable material, or complexed thereto. Applicants respectfully submit that simply because Kumta mentions β-TCP as a byproduct of hydroxyapatite decomposition does not mean that Kumta discloses adsorbing a vector onto a β-TCP bioadaptable material. Kumta discloses delivery of plasmids using only hydroxyapatite, and not a β-TCP bioadaptable material. Therefore, for at least the above reasons, Applicants respectfully submit that Kumta does not disclose or suggest the invention as claimed. Favorable reconsideration is respectfully requested.

Claims 9-12 were rejected under 35 U.S.C. §102(a) and 102(e) as being anticipated by Doll et al. (U.S. Patent Application Publication No. 2003/0235564).

It is the position of the Office Action that Doll discloses the invention as claimed. This rejection is also maintained from the previous Office Action. Doll is directed at compositions and devices comprising the Runx2 protein. Doll discloses using either the Runx2 protein itself, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with a polynucleotide encoding the Runx2 protein. Paragraph [0010]. Doll discloses the use of retroviral and adenoviral vectors at paragraph [0096]-[0098]. The Office Action states that paragraph [0053] discloses the use of β-TCP. Although paragraph [0053] does not disclose this, paragraphs [0052], [0055], [0056], and [0086] appear to disclose the use of tricalcium phosphates.

In the Amendment filed on August 1, 2007, Applicants submitted that while Doll describes the use of some elements of the invention, it does not disclose or suggest the specific constitution of the present invention. That is, Doll does not disclose or suggest "an implant consisting of a bioadaptable porous material on which an adenoviral or retroviral vector carrying a gene encoding an osteo-inducible transcription factor Cbfa1 *is adsorbed.*"

In response, the Office Action repeated the above-referenced comments regarding the term "adsorb." The Office Action thus concludes that the broad disclosure of Doll anticipates claim 9. In response, Applicants respectfully submit that Doll does not disclose or suggest the invention as claimed. The Office Action states that "[i]t is noted that Doll et al. do not teach the

verbatim of the claims recited in the instant application, which Applicant appears to regard as the requirement for the art to be anticipatory."

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814, F.2d 628, 621, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Although the claimed elements need not be described *ipsissimis verbis* ("word for word"), the elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). See also MPEP § 2131.

In the telephone interview of January 11, 2008, Applicants' representative submitted that Doll was silent with respect to how the Runx2 plasmid is incorporated into a bioadaptable material. Essentially, the Examiners argued that while Doll did not specifically disclose adsorption, in the absence of evidence to the contrary, the disclosed composition of Doll would be identical to that of the claimed invention. Examiner Shen noted the "pharmaceutically acceptable carrier," arguing that such a carrier would adsorb water and biomaterials. In the absence of evidence to the contrary, the Examiners presumed that this combination would include adsorption. Specifically, as stated in the Interview Summary dated January 18, 2008, "[c]onsidering a pharmaceutical composition comprises beta-TCP and a polynucleotide encoding Cbfa1 dissolved in water, the claimed adsorption process will inherently occur." In other words, the Examiners appear to be of the position that Doll inherently discloses adsorption of Runx2 onto a pharmaceutically acceptable carrier. Thus, the Examiners were of the position that the composition of Doll would inherently be structurally identical to the claimed implant.

In response, Applicants respectfully submit that Doll does not inherently disclose an implant including the claimed adsorption. Doll does not explicitly describe how Runx2 is incorporated into a porous material. However, Applicants respectfully submit that specific procedures must be undertaken in order to ensure adsorption. An example of one such procedure resulting in adsorption is discussed in the following passages of the specification. Page 7, lines 15-22:

> Such soaking may be carried out under reduced pressure according to need, so that the vector-containing solution is sufficiently diffused throughout the bioadaptable materials. For example, a viral vector solution (1×10^8 to 10^9 pfu/ml) is diluted with an adequate serum-free solvent (e.g., isotonic sodium chloride solution) or medium, and a block of bioadaptable materials is soaked therein. The inside of the block is degasified under a reduced pressure of 100 to 150 mmHg to allow the viral vector solution to thoroughly fill the block. (emphasis added).

Page 11, lines 7-9:

> RBMO harvested by trypsin treatment, the cell density was adjusted to 1,000,000 cells/ml, and the cells were allowed to adsorb onto the block under reduced pressure (100 mmHg). (emphasis added).

Page 11, lines 15-17:

> A β-TCP block (2 mm × 2 mm × 2 mm, Olympus) or a hydroxyapatite (HA) block (2 mm × 2 mm × 2 mm, Interpore) was soaked in a mixed solution of recombinant adenoviruses of Cbfa1 and Cre recombinase genes (1×10^9 pfu/ml) for 3 hours.

Page 16, lines 13-15:

> The OPLA composite was soaked in a mixed solution of Adv-Cbfa1 and Ade-cre recombinant adenoviruses (1×10^9 pfu/ml) for 2 minutes during degasification under reduced pressure, and it was then allowed to stand for 3 hours or longer. (emphasis added).

As support of the above remarks, Applicants herewith submit Dong et al. 2002 and Dong et al. 2001, both of which show that a low-pressure system results in osteogenesis of mesenchymal stem cells with high efficiency.

On the other hand, if a high-pressure environment is present, adsorption will not take place. In other words, Adv-Cbfa1 cannot be adsorbed into a porous material with a large amount of air inside simply by soaking in the high pressure environment of Doll. Rather, one way to achieve adsorption is to soak the porous material in a solution containing Adv-Cbfa1 under reduced pressure so that the Adv-Cbfa1 will infiltrate into the pores of the porous material in a manner consistent with adsorption.

However, Doll does not disclose or suggest these required procedures. Rather, Doll describes at paragraph [0067] that:

> injecting a suspension of cells in a polymer solution improves the reproducibility of cell seeding throughout a device, and protects the cells from shear forces or pressure induced necrosis, and aids in defining the spatial location of cell delivery. (emphasis added).

In other words, the cells are subjected to a high pressure during the course of incorporating the Runx2 into the porous material. As such, adsorption cannot occur.

According to MPEP § 2112, in order for a claim feature to be inherently, there must be provided a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent feature is "*necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Moreover, MPEP §2112 further states that "inherency...may not be established by probabilities or possibilities" and "the mere

fact that a certain thing may result from a given set of circumstances is not sufficient." Thus, since the conditions necessary to give rise to adsorption are not present in Doll, Doll does not inherently or explicitly disclose adsorption.

In other words, a low-pressure environment necessarily gives rise to adsorption, and a high-pressure environment necessarily gives rise to non-adsorption. Accordingly, Applicants respectfully submit that Doll does not disclose or suggest the invention as claimed. However, Applicants clarify that adsorption is not necessarily the result of a low-pressure environment, since other procedures may result in adsorption. Favorable reconsideration is respectfully requested.

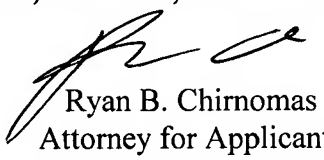
For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP



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RBC/nrp
Enclosures: Dictionary Definition of "adsorption"

Dong et al. "Long-term durability of porous hydroxyapatite with low-pressure system to support osteogenesis of mesenchymal stem cells." Biomed Mater Eng. 2002, 12(2): 203-209.

Dong et al. "Application of low-pressure system to sustain in vivo bone formation in osteoblast/porous hydroxyapatite composite." Materials Science and Engineering 2001 17: 37-43.